SGLT2 inhibitors in patients with CKD and co-morbidities

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Conflicts of interest

Au cours des quatre dernières années, j'ai eu une affiliation ou des intérêts (financiers ou de nature non-pécuniaire) avec la ou les société(s) suivante(s) :

- Astrazeneca, Bayer, Boehringer, Cardiostory, Echosens, Lilly, Novonordisk, Novartis, NP Medical

SGLT2 inhibitors in patients with CKD/renal dysfunction and co-morbidities

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Kidney dysfunction, the metastasis of HF

VIEWPOINT

Heart Failure

TNM-Like Classification

Francesco Fedele, MD, Paolo Severino, MD, Simone Calcagno, MD, Massimo Mancone, MD, PhD

Rome, Italy

Heart	Lung	Malfunction of Other Organs
H-1: impaired systolic or diastolic function of LV without structural damage	**L-0:** no lung involvement **L-1:** Hemodynamic congestion **L-2:** Clinical congestion **L-3:** Cardiac lung*	**M-0:** no malfunction of other organs **M-1:** single organ damage due to HF **M-2:** double organ damage due to HF **M-3:** multiple organ damage
H-2: LV with systolic or diastolic dysfunction and structural damage (hypertrophy, previous myocardial infarction)		
H-3: systolic and diastolic dysfunction (and/or EF< 35%) with left ventricular remodeling	**Parameters of pulmonary damage:** -Precapillary pulmonary hypertension (mPAP > 25mmHg ; PAWP < 15mmHg) -Post-capillary pulmonary hypertension (mPAP > 25mmHg; PAWP > 15mmHg) -Pleural effusion -Pulmonary edema	**Other Organs:** - Kidney - Liver - Central nervous system
H-4: biventricular systolic and diastolic dysfunction		

JACC 2014

Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies

Risk factor	Addition to risk score								Risk score
Ejection fraction (%)	<20 +7	20–24 +6	25–29 +5	30–34 +3	35–39 +2	40+ 0			
Extra for age (years)	<55	56–59	60–64	65–69	70–74	75–79	80+		
EF < 30	0	+1	+2	+4	+6	+8	+10		
EF 30 - 39	0	+2	+4	+6	+8	+10	+13		
EF 40 +	0	+3	+5	+7	+9	+12	+15		
Extra for Systolic blood pressure (mm Hg)	<110	110–119	120–129	130–139	140–149	150+			
EF < 30	+5	+4	+3	+2	+1	0			
EF 30 - 39	+3	+2	+1	+1	0	0			
EF 40 +	+2	+1	+1	0	0	0			
BMI (kg / m^2)	<15 +6	15–19 +5	20–24 +3	25–29 +2	30+ 0				
Creatinine (µmol/l)	<90 0	90–109 +1	110–129 +2	130–149 +3	150–169 +4	170–209 +5	210–249 +6	250+ +8	
NYHA Class	1 0	2 +2	3 +6	4 +8					
Male				+1					
Current smoker				+1					
Diabetic				+3					
Diagnosis of COPD				+2					
First diagnosis of heart failure in the past 18 months				+2					
Not on beta blocker				+3					
Not on ACEI/ARB				+1					
								Total risk score =	

Creat >250 micromol/l versus <90 : + 8 points

As being **79 y.o. versus <55 y.o.** !
Or being **NYHA IV versus I** !

MORE than **LVEF <20% versus >40%** !

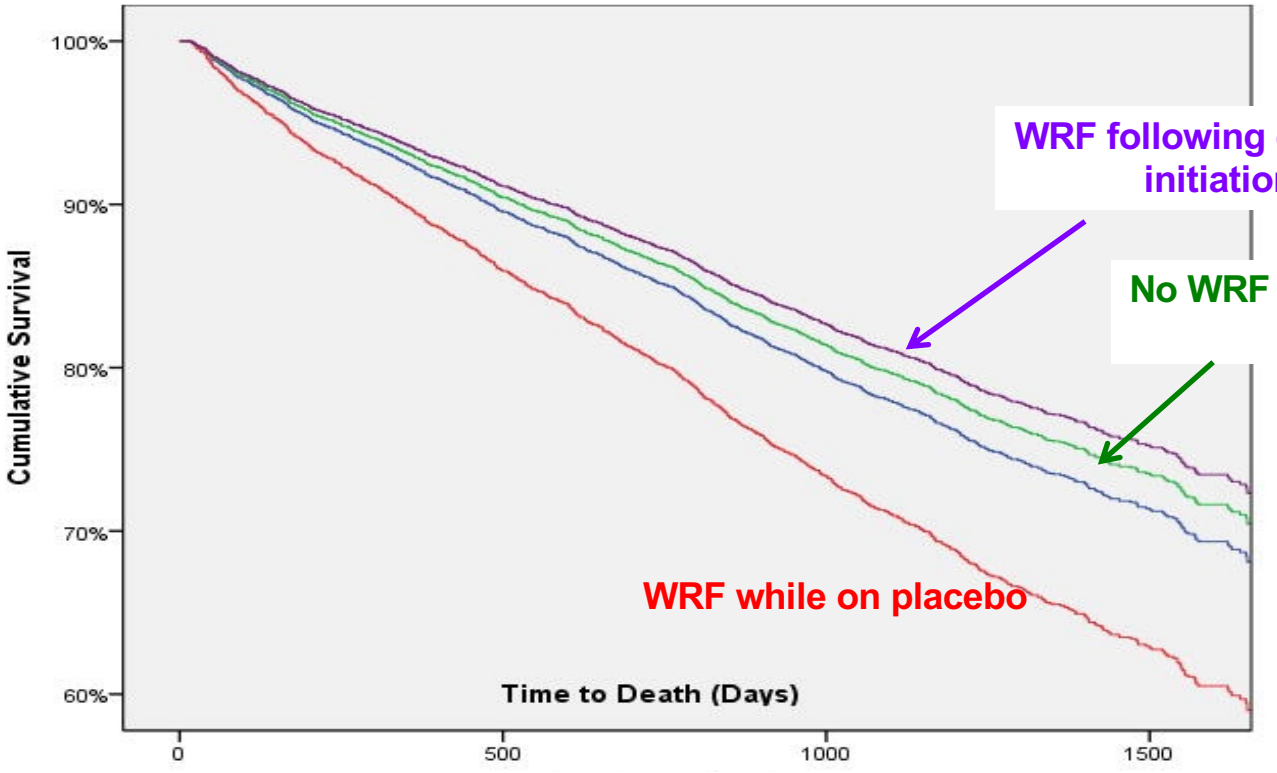
Kidney function has a MAJOR prognostic role

However, changes in renal function have LESS prognostic power than initial/baseline/"true" renal function.

European Heart Journal (2013) **34**, 1404–1413
doi:10.1093/eurheartj/ehs337

But kidney dysfunction is not always bad !

SOLVD trial reanalysis - ACEi in HFrEF
Patient survival according to WRF/noWRF after ACEi/placebo initiation



Worsening renal function is almost good news while optimizing HF treatment !

Testani *et al.*, 2011

The worst, stoping all HF drugs !

Unravelling the interplay between hyperkalaemia, renin–angiotensin–aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry

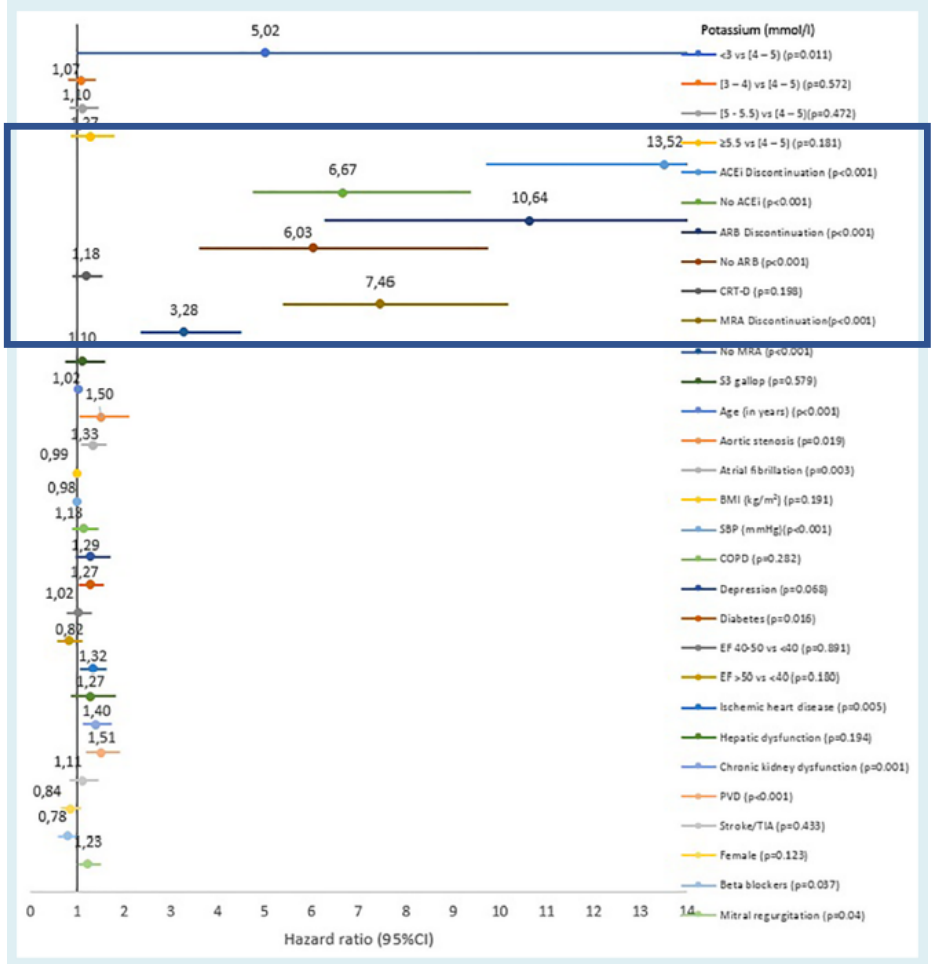
>20% ACEi/ARB discontinuation
>30% MRA discontinuation

In multivariable analysis
Dyskalemia loosly associated with outcome

Important increase in the risk of death after
stopping ACEi (x13)
stopping ARBs (x11)
or MRAs (x3)

SGLT2i not mentionned (2020)
Very likely same results…

Rossignol, EJHF, 2020



Key clinical question for HF physicians is not how to manage CKD and/or worsening renal function

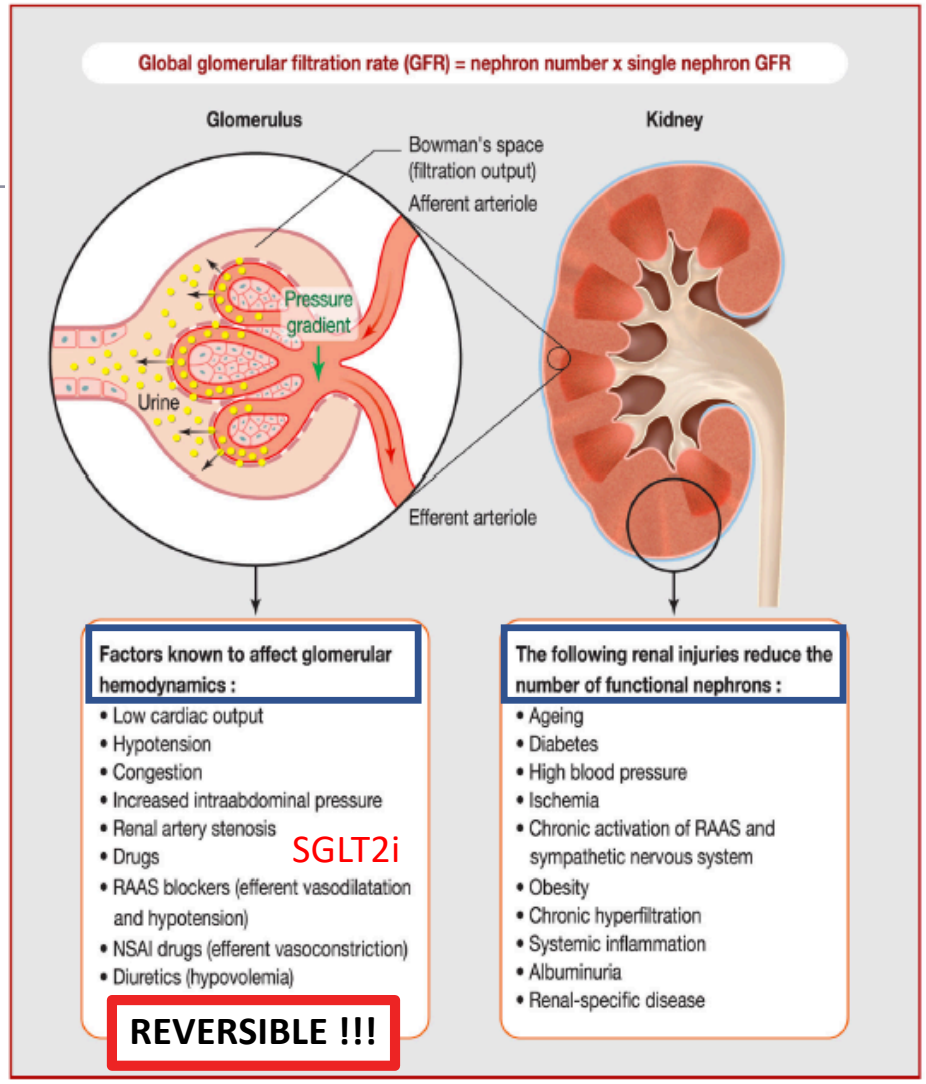
=> How to best manage HF treatments (including SGLT2i) in the frame of CKD and/or worsening renal function

EXPERT CONSENSUS

Practical management of worsening renal function in outpatients with heart failure and reduced ejection fraction: Statement from a panel of multidisciplinary experts and the Heart Failure Working Group of the French Society of Cardiology

Prise en charge pratique de l'aggravation de fonction rénale chez les patients ambulatoires atteints d'insuffisance cardiaque à fraction d'éjection altérée: position d'un groupe multidisciplinaire d'experts et du Groupe Insuffisance Cardiaque et Cardiomyopathie (GICC) de la Société Française de Cardiologie

Nathan Mewton[a,1], Nicolas Girerd[b,1], Jean-Jacques Boffa[c], Cécile Courivaud[d], Richard Isnard[e], Laurent Juillard[f], Nicolas Lamblin[g], Matthieu Legrand[h], Damien Logeart[i], Christophe Mariat[j], Edith Meune[k], Pierre Sabouret[l], Laurent Sebbag[a], Patrick Rossignol[b,*]



Mewton, Girerd, …, Rossignol, ACVD, 2020

The heart and the kidney: a complex relationship

HF specialist point of view

« Organic » and/or « Chronic » kidney dysfunction is bad

= CKD

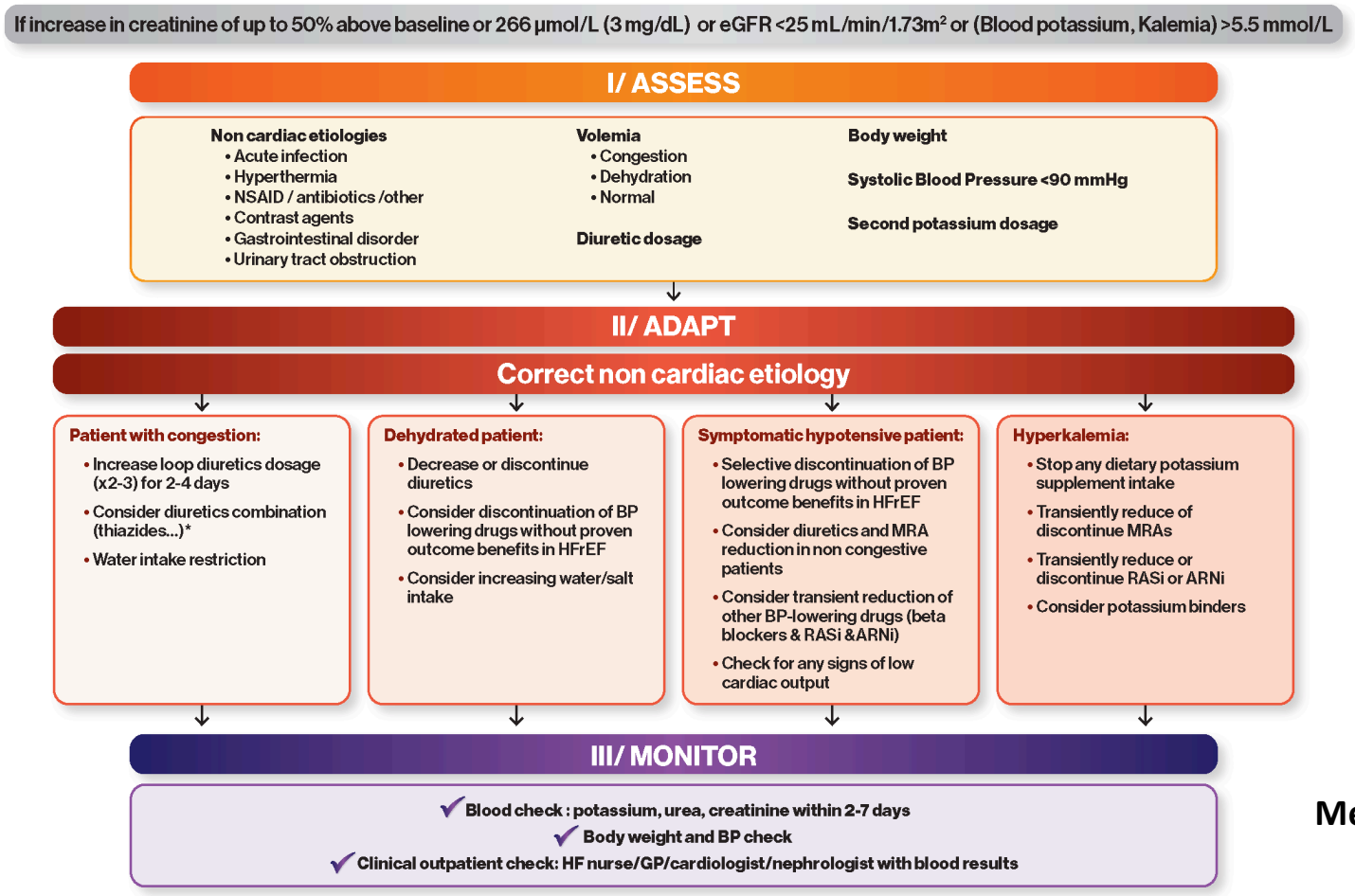
Renal function fluctuations while uptitrating HF drugs is nowhere near as bad

AND SHOULD NOT PREVENT OPTIMAL HF TREATMENT !!!!

Algorithme « GICC »

Algorithm A2M « GICC »

Worsening Renal Failure & Hyperkalemia in HFrEF Outpatients



* Preferably in hospital to monitor urinary output enhancement

SGL2i is not mentioned
But do not need to be mentioned !

Mewton, Girerd, ACVD, 2020

CiC-P
Centre d'Investigation Clinique
Plurithématique - Nancy

The cardiorenal synergy with SGLT2i !

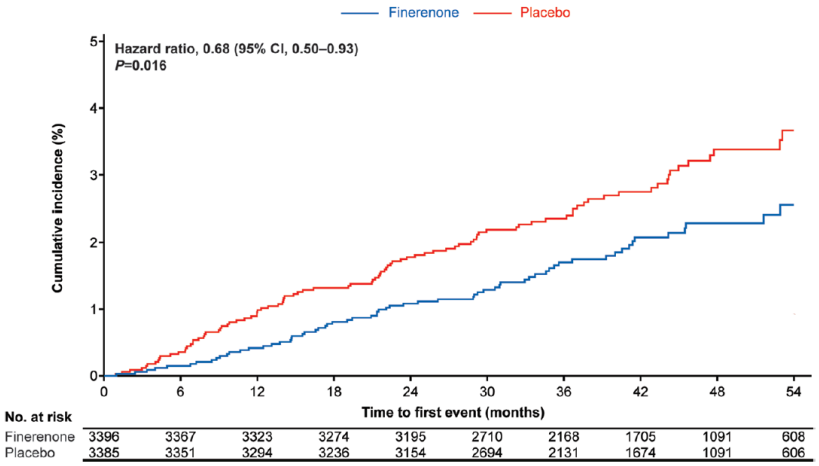
Circulation

ORIGINAL RESEARCH ARTICLE

Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial

Gerasimos Filippatos, MD; Stefan D. Anker, MD, PhD; Rajiv Agarwal, MD, MS; Luis M. Ruilope, MD; Peter Rossing, MD; George L. Bakris, MD; Christoph Tasto, PhD; Amer Joseph, MBBS; Peter Kolkhof, PhD; Andrea Lage, MD; Bertram Pitt, MD; on behalf of the FIGARO-DKD Investigators

Incidence of new onset HF in patients without HF at baseline

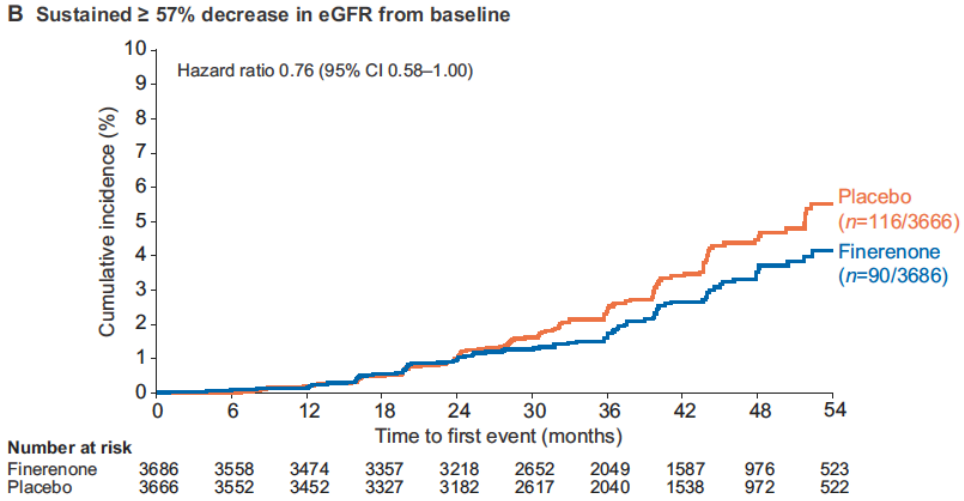


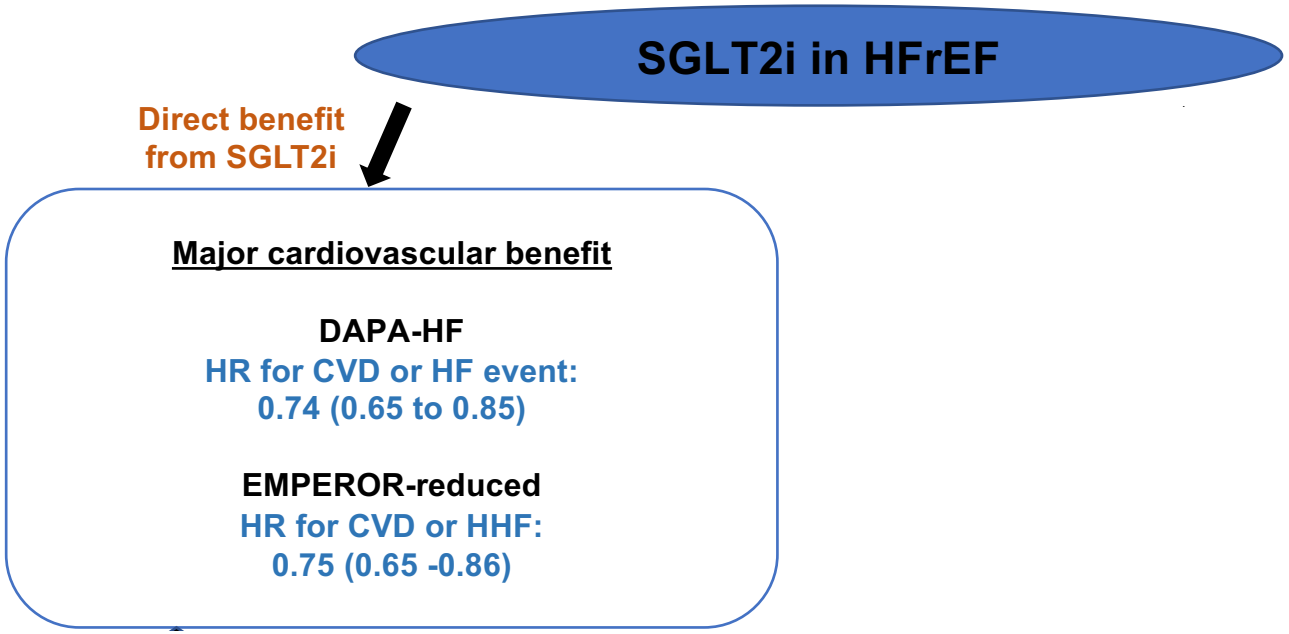
Nephrology Dialysis Transplantation (2022) 0: 1–12
https://doi.org/10.1093/ndt/gfac157
Advance Access publication date 22 April 2022

Kidney outcomes with finerenone: an analysis from the FIGARO-DKD study

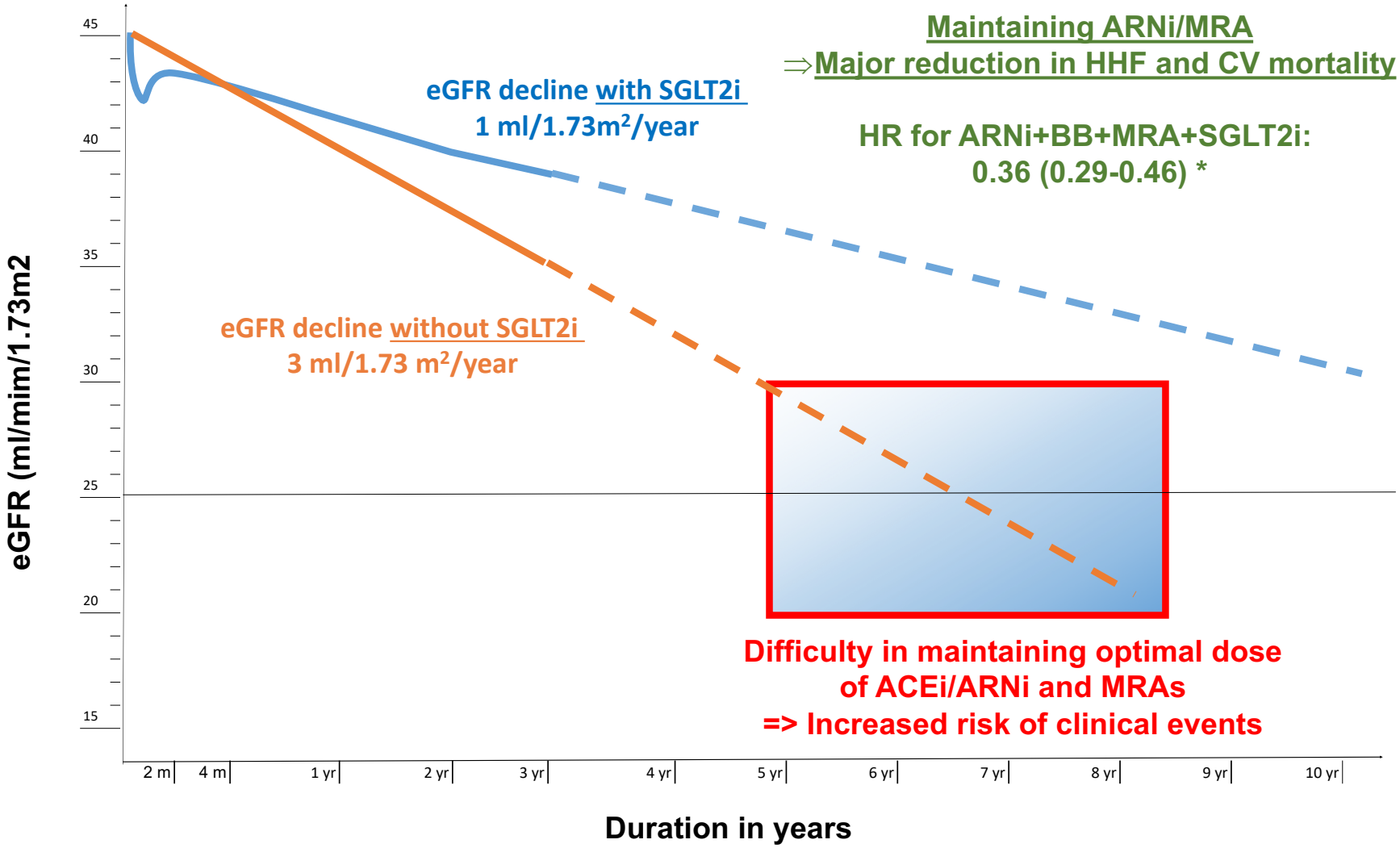
Luis M. Ruilope[1,2,3], Bertram Pitt[4], Stefan D. Anker[5], Peter Rossing[6,7], Csaba P. Kovesdy[8], Roberto Pecoits-Filho[9,10], Pablo Pergola[11], Amer Joseph[12], Andrea Lage[13], Nicole Mentenich[14], Markus F. Scheerer[15], and George L. Bakris[16]; on behalf of the FIGARO-DKD Investigators

Incidence of sustained worsening eGFR





Rastogi, Girerd
Heart Fail Clin. 2022



*Tromp et al., A Systematic A Systematic Review and Network-Meta-Analysis of Pharmacological Treatment of HFrEF; 2021; JACC: HF
Dotted line represents extrapolated eGFR to longer follow-up than available evidence in DAPA-HF and COMMANDER-HF

Rastogi
Girerd
Heart Fail
Clin. 2022

ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 1906–1914
doi:10.1002/ejhf.2638

RESEARCH ARTICLE

Longitudinal trajectories in renal function before and after heart failure hospitalization among patients with heart failure with preserved ejection fraction in the PARAGON-HF trial

Safia Chatur[1†], Muthiah Vaduganathan[1†], Alexander Peikert[1], Brian L. Claggett[1], Finnian R. McCausland[2], Hicham Skali[1], Marc A. Pfeffer[1], Iris E. Beldhuis[3], Lars Kober[4], Petar Seferovic[5], Martin Lefkowitz[6], John J.V. McMurray[7], and Scott D. Solomon[1]*

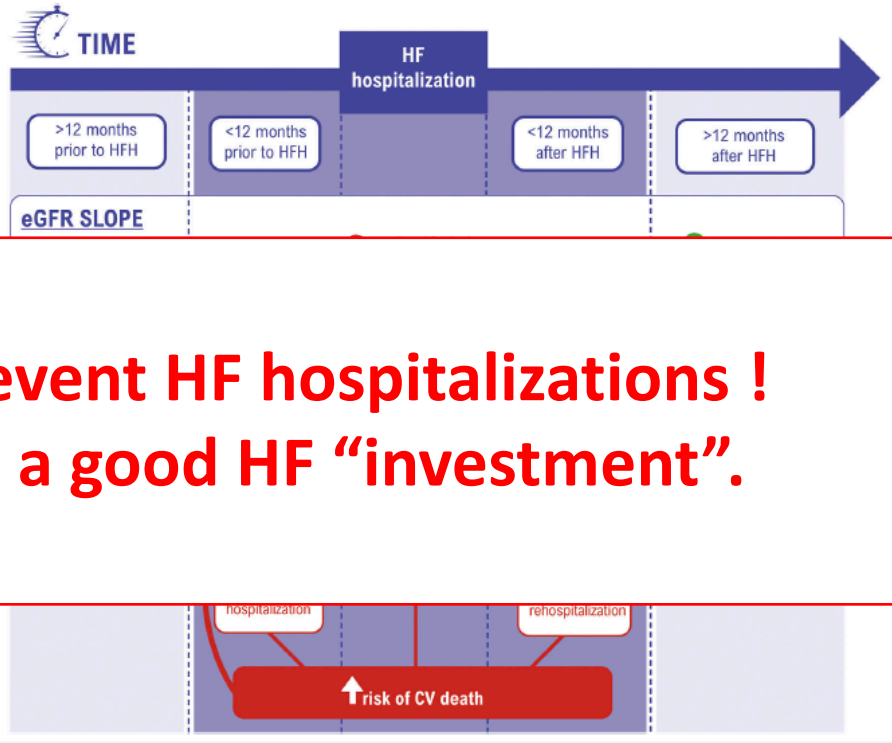
ESC European Society of Cardiology
European Journal of Heart Failure (2022) 24, 1915–1917
doi:10.1002/ejhf.2673

INVITED EDITORIAL

Worsening renal function precedes and follows worsening heart failure

Nicolas Girerd*

Université de Lorraine, INSERM, Centre d'Investigations Cliniques 1433, CHRU de Nancy, Institut Lorrain du Cœur et des Vaisseaux, Nancy, France and INI-CRCT (Cardiovascular and Renal Clinical Trialists) F-CRIN Network, Nancy, France



Preventing WRF may actually prevent HF hospitalizations !
So preserving kidney function is a good HF "investment".

Months Relative to HFH

Months Relative to HFH

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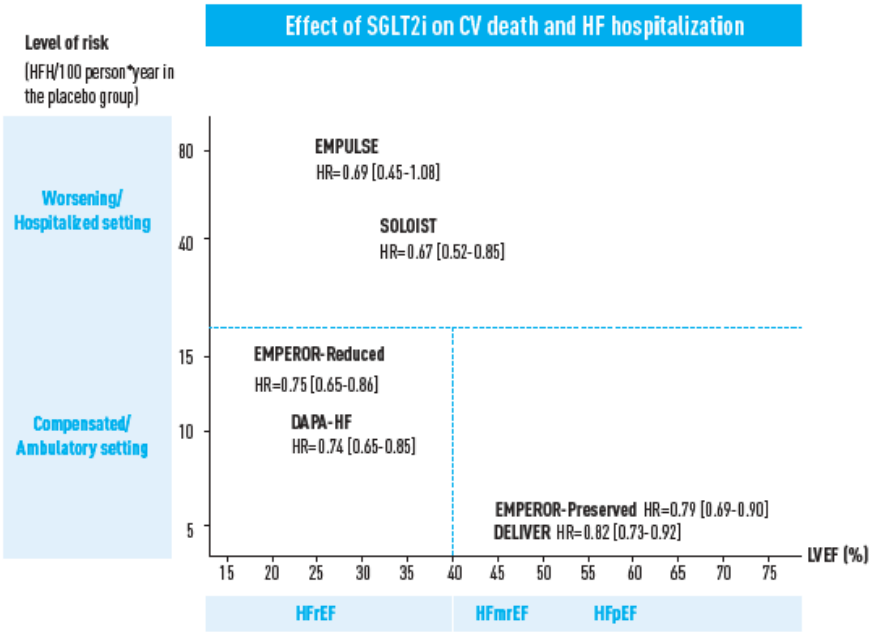
France

In whom should we introduce the treatment ?

Girerd, Zannad, Journal of Internal Medicine, 2023

Homogeneous effect of SGLT2i across the spectrum of heart failure severity and ejection fraction



Good safety profile of SGLT2i in heart failure

Ketoacidosis
HR=0.90 [0.30-2.77]

Amputations
HR=1.00 [0.64-1.55]

Genital infection
HR=2.97 [2.02-4.36] / absolute risk <2%

Acute kidney injury
HR=0.81 [0.58-1.12]

Younes, IJC, 2022

Effect of SGLT2i across the spectrum of heart failure profiles

Disregarding of

Type 2 diabetic status
Ref. DAPA-HF, McMurray NEJM 2019; EMPEROR-Reduced, Packer NEJM 2020; EMPEROR-Preserved, Anker NEJM 2021; DELIVER, Solomon NEJM 2022

Baseline eGFR
(exclusion criteria eGFR<20 ml/min in Empagliflozin trials and <30 ml/min in Dapaglifozin trials)
Ref. DAPA-HF, McMurray NEJM 2019; EMPEROR-Reduced, Packer NEJM 2020; EMPEROR-Preserved, Anker NEJM 2021; DELIVER, Solomon NEJM 2022; DAPA-HF, Jhund Circulation 2021

Baseline blood pressure
(exclusion criteria <100mmHg in Empagliflozin trials and <95 mmHG in Dapaglifozin trials)
Ref. DAPA-HF, Serenelli EHJ 2020; EMPEROR-Reduced, Bohm JACC 2021

Baseline atrial fibrillation
Ref. DELIVER, Butt JACC 2020

Baseline heart rate
Ref. EMPEROR-Preserved, Bohm EJHF 2022

All heart failure patients are eligible for SGLT2i therapy

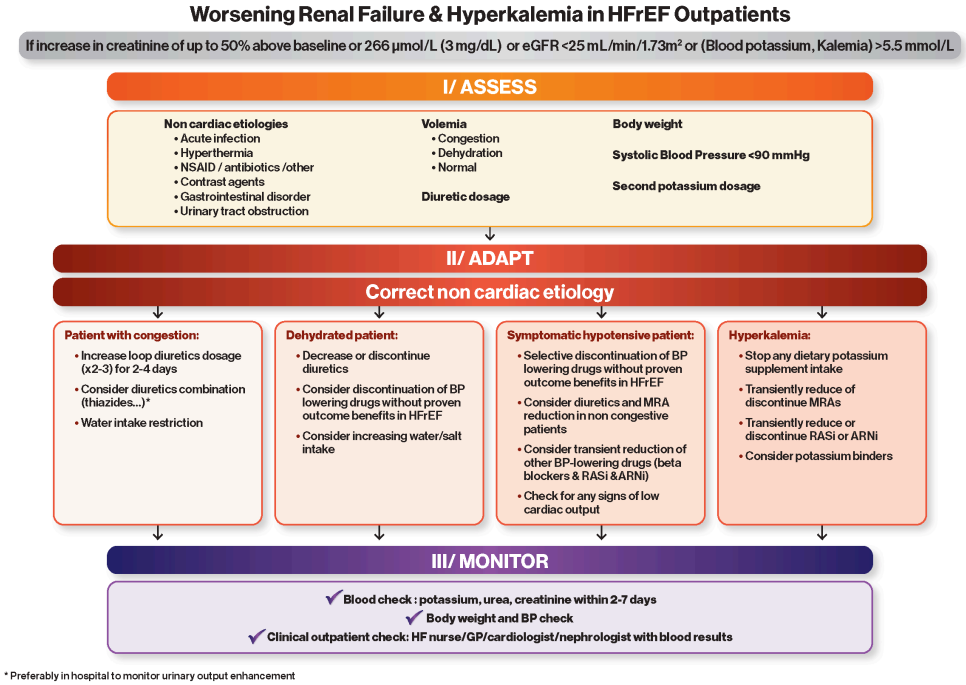
Exception: Type I diabetes

Gaps in evidence: Pregnancy and end-stage renal disease

Only comorbidity which prevents initiation is Type I diabetes….

SGLT2 inhibitors in patients with CKD and co-morbidities

- CKD/renal function in HF is of paramount importance !
- However, do not over-react to worsening renal function, including in patients with CKD
- SGLT2i may increase creatinine on the short-term but are protective for the kidney !!!
- Excellent treatment for patients with HF and CKD !!!
  - From one stone two birds !!!
- The only comorbidity which has an impact on SGLT2i initiation is Type I diabetes



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Merci !

ville de Nancy